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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,965	11/13/2001	Pierre Colas	00786/310001	4646

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
08/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/066,965	COLAS ET AL.	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-65,67,70-78,84 and 93-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-65,67,70-78,84 and 93-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed February 20, 2007 on August 20, 2007 is acknowledged.

Claim Disposition

2. Claims 63-65, 67, 70-78, 84, 93-101 are pending and are under examination.

Maintained and Amended-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 63-65, 67, 70-78, 84 and 93-95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompasses a large variable genus of proteins. The claims encompass a peptide aptamer (intracellular recognition molecule R,) within any cell and any intracellular target; said intracellular recognition molecule R is bound to any TRX-like protein as a platform and comprises "a peptide" of five to sixty amino acids (see claim 63 for example). The claims are drawn also to any peptide recognition molecule having a random peptide (claim 65) or comprise a mutant of for example SEQ ID NO:1 having 1 to 3 amino acid changes (claim 72). Furthermore, the claims are drawn to "any heterologous platform" (claim 67). The specification discloses that using mutagenesis, recognition moieties R, particularly peptide aptamers were prepared (page 8) and a recognition moiety R is any molecule which has the capacity to interact with high specificity and affinity within a cell with a target T (see page 9). However, the only intracellular recognition molecules exemplified are peptide aptamers, for example Cdk2 (see page 12, for example). The platform preferred is thioredoxin, however, the claims are also directed to thioredoxin-like proteins (see claim 63 and page 12 of the specification), however, none is disclosed. In addition, paragraph [0059] of the specification disclose that the "thioredoxin-like proteins have at least 18%, preferably at least 40% and most preferably at least 75% homology with the amino acid sequence of *E. coli* thioredoxin over 80 amino acids", which includes an enormous amount of variability, consequently, the desired effect of bonding of the recognition molecule R to the platform may not occur. The specification lacks adequate written description with

regard to the variable T (target). In addition, the claims are directed to a recognition molecule that can vary in length, hence may not function as desired, knowing that structural changes can affect the structure-function relationship of a protein. No correlation is made between structure and function.

Therefore, the skilled artisan cannot envision the detailed chemical structure of the peptide aptamer and TRX-like protein encompassed in the claims, thus the claimed invention lacks adequate written description. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Moreover, claims 72 and 73 recite a structure for the peptide recognition domain with the open language "comprises or having" thus the recited 20 amino acids in claim 73 could expand to a limitless amount which is well outside the recited "5 to 60" recited in claim 63 or 10-40 in claim 64. Note also claim 72 is broader than claims 63-64 and can have one or more amino acid changes for which no information is provided as to what the change will be or where in

sequence the change will occur or if the change affects contiguous residues. The same issue is found in claim 75, which recites a mutant "having from one to three amino changes" because there is no indication that the changes are contiguous and with the open language the claims read on 1-20 amino acid changes or more based on the fact that the sequence can be longer with the comprising language. With respect to claim 76, the claim recites a structure for the "recognition domain", however does not rectify all the deficiencies of claim 64, encompassing a genus of TRX-like proteins (see also claims 91-92 with respect to the open language and mutants). It is noted that claim 85 defines the platform, however, the claim reads on a genus of peptides and no correlation is made between structure and function.

Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The

compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

4. Claims 63-65, 67, 70-78, 84 and 93-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for intracellular recognition molecules that are peptide aptamer (such as the sequences disclosed on page 33 and anti-Cdk2 and others listed on page 12 of the specification as well as cited in the prior art), does not reasonably provide enablement for any intracellular recognition molecule or target or TRX-like protein (claim 63 for example). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of

the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass a peptide aptamer (intracellular recognition molecule,) and any target bound to any TRX-like protein as a platform interacting with an unspecified amount of targets (see claim 63 for example); any peptide that comprises 5 to 60 amino acids or 10-40 amino acids; and the claims encompass any intracellular recognition molecules and any target bound to any platform having the capacity to interact with the unspecified amount of targets. The claims are also directed to any oligomeric intracellular recognition molecules absent any structural limitations. In claim 85 for example, the claim is broadly drawn to any proteinaceous recognition domain consisting of a peptide of 5 to 60 amino acids. The specification discloses that using mutagenesis, recognition moieties R, particularly peptide aptamers were prepared (page 8) and a recognition moiety R is any molecule which has the capacity to interact with high specificity and affinity within a cell with a target T (see page 9). However, the only intracellular recognition molecules exemplified are peptide aptamers, for example Cdk2 (see page 12, for example). The platform preferred is thioredoxin, however, the claims are also directed to thioredoxin-like proteins (see claim 63 and page 12 of the specification), however, none is disclosed. It is noted also that paragraph [0059] of the specification disclose that the "thioredoxin-like proteins have at least 18%, preferably at least 40% and most preferably at least 75% homology with the amino acid sequence of *E. coli* thioredoxin over 80 amino acids", which includes an enormous amount of

variability, consequently, the desired effect of bonding of the recognition molecule R to the platform may not occur. The specification lacks adequate guidance with regard to the variable T (target). In addition, the claims are directed to a recognition molecule that can vary in length, hence may not function as desired, knowing that structural changes can affect the structure-function relationship of a protein.

Note that the intracellular recognition molecule R comprises a recognition domain which is disclosed as "comprising" (see for example claims 72, 73 and 75) or "consists" (see for example claims 63-64) of peptides with lengths of 5-60 or 10-40, mutations wherein 1-3 amino acid residues are changed or has for example, the amino acid sequence of "QVWSLWALGWRWLRRYGWNM" (see claims 72-73, 75), see also page 60 of the specification. The open and closed language in association with the structure is inconsistent, for example independent claims 64 and 85 recite a peptide length that is closed, however, provides no structure to correlate with a function for the recited peptide. The dependent claims therefrom recite open language with regard to the structure and contemplate mutations with no functional limitations or indication as to whether or not the structure once modified will have biological activity or what the structure will look like. In addition, the preferred peptide is ten to forty amino acids, however, a 20-mer is exemplified. It is also disclosed on page 28 of the specification that the peptide can have a mutant having from one to five, preferably one to three amino acid changes with respect to said sequence and there is no indicia as to a conserved region or where in the sequence the modifications will occur and if said modification can be tolerated in the sequence. Due to the large quantity of

experimentation necessary to generate an intracellular recognition molecule comprising a domain that is variable that can interact with any target and to screen same for activity and the lack of guidance/direction provided in the instant specification with regard to the variables in the invention, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein are unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims as the claims broadly read on intracellular recognition molecule fragments or any target or platform. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in

certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification, as the variables are described in vague terms. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct any intracellular recognition molecule with a variable domain having the capacity to specifically interact with any target.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of intracellular recognition molecules and targets, which may or may not possess the ability to interact. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in

the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test all intracellular recognition molecules encompassed in the claims would constitute undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

5. Claims 63-65, 67, 70-78, 84, 93-101 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite added material, which is not supported by the original disclosure. Claim 63 and the dependent claims hereto (claims 64-65, 67, 70-78, 84, 93-101) recite "conformationally constrained by covalent bonding at both its extremities" and the amendatory language is not supported by the instant specification. The specification provides support for the covalent bonding, but no so support was found for

the bonding occurring at "both extremities". Therefore, the specification lacks adequate written description.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 72-73, 75-76 and 99-101 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claims 72-73, 75-76 and 99-101 are indefinite for the recitation of "...consists of a mutant of the amino acid sequence..., said mutant having from one to three amino acid changes with respect to said sequence" because the claim recites the closed language of "consists of " with the open language "having" which is equivalent to "comprising". It is unclear how the structure can consist of SEQ ID NO:1 for example, and have from one to three amino acid changes (said open language means that more than 3 residues can be changed). Note that MPEP 2111.02 states, "In determining the scope of applicant's claims directed to "a purified oligonucleotide comprising at least a portion of the nucleotide sequence of SEQ ID NO:1, wherein said portion consists of the nucleotide sequence from.... to 2473 of SEQ ID NO:1, and wherein said portion of the nucleotide sequence of SEQ ID NO:1 has promoter activity", the court stated that the use of "consists" in the body of the claims does not limit the open-ended "comprising" language in the claims (Id. at 1257, 73 USPQ2d at 1367).

Response to Arguments

7. The remarks have been considered in full, however, are not persuasive. Note that the rejections under 35 U.S.C. 112, first paragraph written description and enablement of record have been maintained and amended based on amendments made to the claims. As previously stated claim 72 for example, recites a structure for the peptide recognition domain, however, the claim also encompasses a genus of mutants not adequately described or supported by the instant specification, thus rejected under the 112, first paragraph enablement and written description statutes. Note however, that newly submitted claims 96-98 are only rejected based on the new matter written description rejection newly instituted based on applicant's amendments to claim 63. These claims rectify the deficiencies of independent claim 63 thus are not rejected for enablement or written description based on the genus claim language.

Applicant's arguments regarding the newly imported language is claim 63 is noted "at both its extremities", however, note that this language was not found in the specification and does not address the issues raised on claim 63 and its dependents of lacking a structure-function correlation to the large variable genus claimed of protein structures. Applicant also argue that the amendatory language of "consists of" resolves issues raised, however, note that this language in for example claim 72 raises an issue under 35 U.S.C. 112, second paragraph for the reasons stated above. Applicants argue that the art recognizes thioredoxin-like proteins thus traverses the rejections of record,

however, applicant's arguments are not persuasive as the claims are not limited to for example the exemplified thioredoxin platform, but instead include any thioredoxin-like proteins, which are not defined by a structure or guaranteed to maintain a thioredoxin-like activity, nor are the claims limited to those thioredoxin-like proteins found in the art or the instant application. Thus, these claims are properly rejected under the statues above.

Applicant again points to the Colas Declaration submitted and examples provided in the specification. This argument has been considered as well as the declaration, however, the claims are not limited to such exemplification and the arguments do not breathe life into the claims which broadly read on any structure as indicated above. Claim 63 is very broad and is not limited to Cdk2 or bak or to thioredoxin or to SEQ ID NO:2 for example, instead encompass several variables that are unidentified and can vastly change. As previously stated, the issue at hand is that the claims encompass a large variable genus, which is neither adequately described or enabled. As stated above, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*" and "the scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...".

Additionally, the issues raised in the rejections pertain to the claim of a genus of proteins not adequately described or supported by the instant specification. The issue at hand is that the claims are drawn to a genus of peptides with a length of 5-60 amino acids for which no structure is provided, a genus of TRX-like proteins, a genus of

proteinaceous recognition domains, for which no correlation is made between structure and function, thus not adequately described. The instant specification is not commensurate in scope with the claims. As stated above the claims encompass any peptide aptamer and any TRX-like protein, which is not supported by the disclosure, thus not enabled. Therefore, the rejections remain.

Conclusion

8. No claims are presently allowable.

9. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed, can be reached at (571) 272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652